REMARKS

Status

Claims 1-20 were pending in this Office Action. The present response cancels claim 2 and adds new claims 23-28. Accordingly, it is claims 1, 3-20 and 23-28 which are at issue.

The Office Action

In the Office Action mailed May 25, 2010, then pending claims 1-20 were rejected. Specifically, claims 1-20 were rejected under 35 U.S.C. §112, first paragraph. Claims 1-4, 12-16 and 18 were rejected under 35 U.S.C. §102 as being anticipated by U.S. Patent 5,728,373 of Alert. Claims 1-5, 11-16, 18 and 20 were rejected under 35 U.S.C. §102 as being anticipated by U.S. Patent Application Publication 2005/0142092 of Lintner. Claims 1-7, 9, 12 and 14 were rejected under 35 U.S.C. §102 as being anticipated by U.S. Patent 6,805,878 of Li. Claims 11 and 19-20 were rejected under 35 U.S.C. §103 as being unpatentable over Alert. Claims 10 and 19 were rejected under 35 U.S.C. §103 as being unpatentable over Lintner.

The Present Invention

The present invention is based upon the surprising finding that ACE inhibitor and/or angiotensin II receptor antagonists act to reduce the visible signs of fine lines and other wrinkling on the skin. This effect has not previously been noted in the art. While not wishing to be bound by speculation, Applicant hypothesizes that this class of materials may reduce the formation of uneven collagen deposits in aging and prematurely aged skin thus evening out skin texture. Thus, the present invention is directed to the general and broad concept of using ACE inhibitors and/or angiotensin II receptor antagonists for reducing skin wrinkling.

The Rejection under 35 U.S.C. §112, First Paragraph

Claims 1-20 were rejected under 35 U.S.C. §112 as not being fully enabled by the present application. In making this rejection the Examiner acknowledges that the specification does describe treatment of the skin with particular materials, but holds that the teaching therein is not sufficient to enable the use of members of the general class of ACE inhibitors and/or angiotensin II receptor antagonists for the claimed purpose.

Applicant respectfully disagrees with the Examiner's position. The present invention, as noted above, is based upon Applicant's surprising finding that materials acting as ACE inhibitors or as angiotensin II receptor antagonists will also function to reduce the visible signs of fine wrinkles. This effect appears to be the result of these materials acting to reduce the uneven collagen deposits in the skin. As such, one of skill in the art (as noted by the Examiner a technically competent M.D. or Ph.D. degreed person) would comprehend the meaning of the broad class of materials and be able to use such materials for the claimed purpose.

Thus, the skilled person will without undue experimentation be able to identify ACE inhibitors and/or angiotensin II receptor antagonists. In fact ACE inhibitors and/or angiotensin II receptor antagonists constitute well recognised classes of drugs. For example, ACE inhibitors and angiotensin receptor antagonists are described as specific classes of compounds in Katzung et al. in Basic & Clinical Pharmacology, which is a well known and widely used textbook regarding basic pharmacology. An entire section of Chapter 11 (p. 170-172) (attached hereto as Exhibit A) describes "Inhibitors of angiotensin" and states that there are "two classes ...: the ACE inhibitors and the competitive inhibitors of angiotensin at its receptors". Also according to the ATC drug ACE inhibitors and angiotensin-II antagonists constitute specific classes of drugs. Thus, the class C9A R1966 is designated "ACE inhibitors", whereas the class C9C I1996 is

designated "Angiotensin-II antagonists". The ATC drug classification is an internationally recognised classification system maintained by the WHO Collaborating Centre for Drug Statistics Methodology in Oslo, Norway and it is recommended by the WHO for international comparisons.

In view of the foregoing, Applicant respectfully submits that one of skill in the art could readily identify, obtain, and employ ACE inhibitors and/or angiotensin II receptor antagonists for the claimed purpose of reducing wrinkling and/or visible signs of fine lines on the skin. Reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph, is respectfully requested.

By the present amendment, Applicant has presented herewith new claims 23-28 directed to specific therapeutic materials. These claims are fully supported in the specification as originally filed and avoid any rejections under 35 U.S.C. §112, first paragraph. Specifically, claims 23 and 25 are directed to compositions and methods employing captopril while claims 24 and 26 are similarly directed to compositions and methods employing enalaprilat. Claims 27 and 28 are directed to methods employing specific compounds listed in the specification.

The Rejections under 35 U.S.C. §102

1. The Rejections Based upon U.S. Patent 5,728,373 of Alert.

Claims 1-4, 12-16 and 18 were rejected as lacking novelty in view of the Alert patent. Alert et al. relates to sunscreen compositions used to prevent the damaging effects of UV light. It is described by Alert et al. that thiol and/or thiol derivatives are added to remedy the disadvantages of the prior art (see col. 2, lines 11-14, US 5,728,373). The disadvantages of the prior art are described as being lack of photostability, difficulties with incorporating light protection agents into formulations, known light protection agents are pure UV-absorbing agents

unsuitable as agents which trap free radicals, and low antioxidant action (see col. 1, line 41 to col. 2, line 9).

Alert et al. furthermore describes that the disclosed formulations are suitable for prophylaxis and/or treatment of UV-induced skin damage (see col. 2, lines 44-45) or the protection or prophylaxis against UV-induced hair damage (see col. 2, lines 50-51).

The thiol or thiol derivatives of Alert et al. are NOT described to reduce, remove or otherwise treat existing "wrinkles" or "visible signs of fine lines on the skin".

There are several differences between different types of changes to the skin. The skilled person within the field of dermatology will be well aware that the mechanisms behind UV/light induced damages to the skin and an age induced ageing are highly different.

First of all the UV induced damages occur due to prolonged UV exposure whereby the structure and function of both the epidermal and dermal tissue are altered. The epidermal thickness is increased due to hyperplasia, and the dermis is affected by a degeneration of collagen and a deposition of abnormal elastotic material. The UV damaged skin can be said to be in a state of chronic inflammation. This is contrary to the age induced ageing where the epidermal and dermal thickness are decreased due to athropy, giving a more prominent vasculature, loss of elasticity, and an increased fragility of the skin.

Accordingly, ageing of the skin, such as for example fine lines or wrinkling, is not necessarily an exhibition of skin damage caused by UV radiation. Skin ageing including fine lines and wrinkling may as well be caused by other mechanisms independent of UV radiation during the natural ageing process and the hereby provided changes to the underlying skin structures.

The person skilled in the art will furthermore be aware that protection from UV damages relies on preventive measures such as keeping out of the sun and using sunscreens. Likewise will the person skilled in the art be aware that prevention of age related ageing of the skin relies on healthiness, i.e. food, rest, exercise, no-smoking, no-drugs etc. Whereas the treatment of already present fine lines or wrinkles will have to focus on the connective tissue in the dermal and epidermal layers or the underlying physiological conditions such as the vascular tissue.

The fact that poor skin tone may in some instances be the result of UV damages is by no means the same as a UV-protective effect obtained by a sunscreen formulation, may reduce or treat already existing fine lines or wrinkles.

The present invention relates to methods of reduction of the visible signs of fine lines on the skin using an ACE inhibitor and/or angiotensin II receptor antagonist (see claim 1) or to methods of treating wrinkles using an ACE inhibitor and/or angiotensin II receptor antagonist. Thus, the present invention provides methods for reducing or treating existing fine lines or wrinkles, whereas Alert et al. teaches prevention of light-induced damages.

The thiol or thiol derivatives of Alert et al. are NOT described as being effective to reduce, remove or otherwise treat existing "wrinkles" or "visible signs of fine lines on the skin", and Alert et al. furthermore does not teach or suggest or hint that the sunscreen composition may be used for this purpose.

Accordingly, claim 1 and claim 15 as well as claims dependent thereon are novel over Alert et al. Reconsideration and withdrawal of this rejection is respectfully requested.

2. The Rejections Based upon U.S. Patent Application Publication 2005/0142092 of Lintner.

Claims 1-5, 11-16, 18 and 20 were rejected under 35 U.S.C. §102 as lacking novelty in view of the Lintner patent application. Lintner et al. relates to cosmetic or dermopharmaceutical compositions which are used to reduce bags and circles under the eyes (see title). In the abstract it is stated that the compositions are used "to treat the visible signs of ageing and fatigue, such as bags and circles under the eyes". It is explicitly described in Lintner that the aim of the invention is to resolve the problem of bags [under the eyes] by acting simultaneously on water retention, inflammation, capillary fragility, and slackening of the cutaneous tissues by a synergistic combination of three active substance categories, i) hesperidins, ii) peptide inhibitors of angiotension I and II converting enzymes, and iii) imunomodulating peptides, immunoglublin fragments (see section [0015]).

The mechanism behind the use of inhibitors of angiotension I and II converting enzymes in the compositions according to Lintner is described as follows: the lympdrainage is stimulated by bradykinin, which again is modulated and degraded by ACE. It is described that dipeptides, especially Val-Trp, are known to inhibit ACE, and therefore increase bradykinin and the lymph drainage, thus removing noxious fluids etc. from the skin (see section [0023]). Thus, it is described that the Val-Trp peptide acts against water retention, sodium imbalance, and oedemas, thereby acting against bags under the eyes (see section [0024]).

Accordingly, Lintner discloses a combination product which synergistically together with hesperidin and oligopeptides acts to reduce bags and circles under the eyes; the effect is documented by the use of H-Val-Trp-OH only. The component ii) ACE inhibitors are disclosed as having an affect against water retention, sodium imbalance and oedemas.

In contrast, the present invention relates to a method of reducing fine lines on the skin or treating wrinkles. The effect disclosed by Lintner et al. is most unsuitable for treatment of wrinkles as wrinkled skin is well known to the skilled person to be thin and dry. Accordingly, water retention should in general not be inhibited when treating wrinkles.

Thus based on the teaching of Lintner it is very surprising that ACE inhibitors and/or angiotensin II receptor antagonists would be considered to be useful for reducing fine lines on the skin or for treating wrinkles.

Nowhere does Lintner et al. describe or suggest any methods of reducing, removing or otherwise treating existing wrinkles or "visible signs of fine lines on the skin".

Accordingly, claim 1 and claim 15 as well as claims dependent thereon are novel over Lintner et al. Reconsideration and withdrawal of these rejections is respectfully requested.

3. The Rejections Based upon U.S. Patent 6,805,878 of Li.

Claims 1-7, 9, 12 and 14 were rejected under 35 U.S.C. §102 as being anticipated by the Li patent. Li et al. relates to transdermal administration of ACE inhibitors (see Title). The document describes dermal compositions able to deliver a therapeutically effective amount of a pharmaceutically active form of an ACE inhibitor (see col. 2, l. 51-58). The compositions may be used in treatment of conditions such as hypertension, heart failure, myocardial infarction and nephropathy (see col. 3, l. 54-57).

Nowhere does Li et al. describe or suggest any methods of reducing, removing or otherwise treating existing wrinkles or "visible signs of fine lines on the skin".

Accordingly, claim 1 and claim 15 as well as claims dependent thereon are novel over Li et al. Reconsideration and withdrawal of these rejections is respectfully requested.

The Rejections under 35 U.S.C. §103

1. The Rejections Based upon Alert.

Claims 11 and 19-20 were rejected under 35 U.S.C. §103 as being unpatentable over Alert. It is the Examiner's opinion that the dosing levels and treatment regimens specified in these claims would be obvious to one of skill in the art in view of the general teaching of Alert. Applicant respectfully submits that in view of the general inapplicability of Alert as discussed above, these rejections are likewise without merit. Reconsideration and withdrawal thereof is respectfully requested.

2. The Rejections Based upon Lintner.

Claims 10 and 19 were rejected under 35 U.S.C. §103 as being obvious in view of Lintner. It is the Examiner's opinion that in view of the general teaching of Lintner it would be obvious to one of skill in the art to utilize a combination of active ingredients and/or administer treatment at least once daily. In view of the general inapplicability of Lintner as discussed above, these rejections are overcome. Reconsideration and withdrawal thereof is respectfully requested.

Claims 8 and 17 Are Further Allowable

Applicant notes for the record that claim 8, which recites that the composition includes at least one angiotensin II receptor antagonist, and claim 17, which recites that the ACE inhibitor and/or angiotensin II receptor antagonist is lisinopril, are not subject to any prior art based rejection. In view of Applicant's remarks with regard to the rejections under 35 U.S.C. §112, first paragraph, these claims are allowable. Applicant further notes for the record that claim 17, which specifically recites the use of lisinopril, is, per se, fully enabled and supported in the specification as originally filed and hence is in condition for allowance.

Conclusion

In view of the foregoing amendments and remarks, Applicant respectfully submits that this application, together with all presently pending claims, is in condition for allowance. Any questions, comments, or suggestions which the Examiner may have should be directed to the undersigned attorney.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 07-1180.

Dated:

Respectfully submitted,

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sation, it is recommended that short-acting nifedipine not be used for hypertension. In any case, sustained-release calcium blockers or calcium blockers with long half-lives provide smoother blood pressure control and are more appropriate for treatment of chronic hypertension. Intravenous nicardipine has recently been released for the treatment of hypertension when oral therapy is not feasible, though parenteral verapamil and diltiazem could be used for the same indication. Nicardipine is typically infused at rates of 2–15 mg/h. Oral short-acting nifedipine has gained some popularity in emergency management of severe hypertension.

INHIBITORS OF ANGIOTENSIN

Although the causative roles of renin, angiotensin, and aldosterone in essential hypertension are still controversial, there do appear to be differences in the activity of this system among individuals. When controlled for daily sodium intake (assessed as 24-hour urinary sodium excretion) and serum potassium concentration, approximately 20% of patients with essential hypertension have inappropriately low and 20% have inappropriately high plasma renin activity. Blood pressure of patients with high-renin hypertension responds well to beta-adrenoceptor blockers, which lower plasma renin activity, and to angiotensin inhibitors—supporting a role for excess renin and angiotensin in this population.

Mechanism & Sites of Action

Renin release from the kidney cortex is stimulated by reduced renal arterial pressure, sympathetic neural stimulation, and reduced sodium delivery or increased sodium concentration at the distal renal tubule. Renin acts upon renin substrate, an α_2-globulin, to split off the inactive decapeptide angiotensin I. Angiotensin I is then converted, primarily by endothelial angiotensin-converting enzyme (ACE) in the lung, to the arterial vasoconstrictor octapeptide angiotensin II (Figure 11–6), which is in turn converted in the adrenal gland to angiotensin III. Angiotensin II has vasoconstrictor and sodium-retaining activity. Angiotensin II and III both stimulate aldosterone release. Angiotensin may contribute to maintaining high vascular resistance in hypertensive states associated with high plasma renin activity, such as renal arterial stenosis, some types of intrinsic renal disease, and malignant hypertension, as well as in essential hypertension after treatment with sodium restriction, diuretics, or vasodilators.

New evidence suggests that a parallel system for angiotensin generation exists in several other tissues (eg, heart) and may be responsible for trophic changes such as cardiac hypertrophy. The converting enzyme involved in tissue angiotensin II synthesis is also inhibited by the ACE inhibitors.

Two classes of drugs act specifically on the renin-angiotensin system: the ACE inhibitors and the competitive inhibitors of angiotensin at its receptors, including losartan, valsartan, and saralasin (saralasin is no longer in clinical use).

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS

Captopril (Figure 17–3) and other drugs in this class inhibit the converting enzyme peptidyl dipeptidase that hydrolyzes angiotensin I to angiotensin II and (under the name plasma kininase) inactivates bradykinin, a potent vasodilator, which works at least in part by stimulating release of nitric oxide and prostacyclin. The hypotensive activity of captopril probably results both from an inhibitory action on the renin-angiotensin system and a stimulating action on the kallikrein-kinin system (Figure 11–6).

Enalapril (Figure 17–3) is a prodrug that is converted by deesterification to a converting enzyme inhibitor, enalaprilat, with effects similar to those of captopril. Enalaprilat itself is available only for intravenous use, primarily for hypertensive emergencies. **Lisinopril** is a lysine derivative of enalaprilat. **Benazepril, fosinopril, moexipril, quinapril,** and **ramipril** are more recently introduced long-acting members of the class. All are prodrugs, like enalapril, and are converted to the active agents by hydrolysis, primarily in the liver.

Angiotensin II inhibitors lower blood pressure principally by decreasing peripheral vascular resistance. Cardiac output and heart rate are not significantly changed. Unlike direct vasodilators, these agents do not result in reflex sympathetic activation and can be used safely in persons with ischemic heart disease. The absence of reflex tachycardia may be due to downward resetting of the baroreceptors or to enhanced parasympathetic activity.

Although converting enzyme inhibitors are most effective in conditions associated with high plasma renin activity, there is no good correlation among subjects between plasma renin activity and antihypertensive response. Accordingly, renin profiling is unnecessary.

ACE inhibitors have a particularly useful role in treating patients with diabetic nephropathy, diminishing proteinuria and stabilizing renal function (even in the absence of lowering of blood pressure). These benefits probably result from improved intrarenal hemodynamics, with decreased glomerular efferent arteriolar resistance and a resulting reduction of intraglomerular capillary pressure. ACE inhibitors have also proved to be extremely useful in the treatment of congestive heart failure, and after myocardial infarction. In the latter case, ACE inhibitors result in better preservation of left ventricular function in the years following infarction, acting by reducing postinfarction myocardial remodeling. These applications are discussed in Chapter 13.

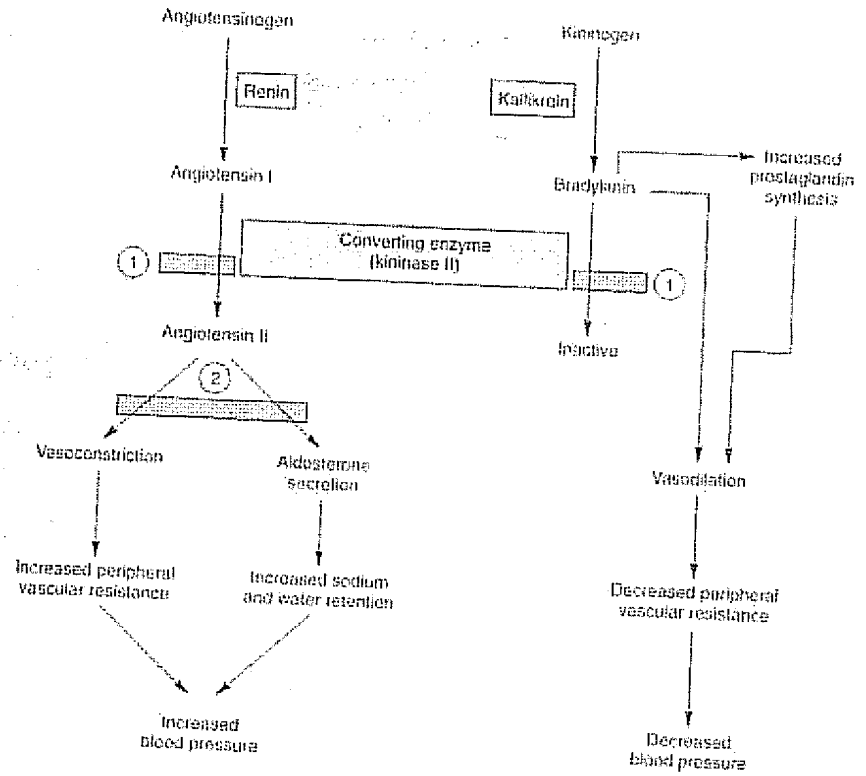

Figure 11–6. Sites of action of ACE inhibitors and receptor blockers. ① Site of ACE blockade. ② Site of receptor blockade.

Pharmacokinetics & Dosage

Captopril is rapidly absorbed, with a bioavailability of about 70% after fasting. Bioavailability is decreased by 30–40% if the drug is taken with food; however, the antihypertensive action of captopril is unaffected. It is metabolized chiefly to disulfide conjugates with other sulfhydryl-containing molecules. Less than half of an oral dose of captopril is excreted unchanged in the urine. Captopril is distributed to most body tissues, with the notable exception of the central nervous system. The half-life of captopril is less than 3 hours. Blood levels correlate poorly with clinical response (see Figure 3–6).

Captopril is initially administered in doses of 25 mg 2 or 3 times each day, 1–2 hours before meals. Maximal blood pressure response is seen 2–4 hours after the dose. At 1- to 2-week intervals, doses can be increased until blood pressure is controlled.

Peak concentrations of enalaprilat occur 3–4 hours after dosing with enalapril. The half-life of enalaprilat is about 11 hours. Typical doses of enalapril are 10–20 mg once or twice daily.

Lisinopril is slowly absorbed, with peak blood levels at about 7 hours after a dose. It has a half-life of 12 hours. Doses of 10–80 mg once daily are effective in most patients.

All of the ACE inhibitors except fosinopril and moexipril are eliminated primarily by the kidneys; doses of these drugs should be reduced in patients with renal insufficiency.

Toxicity

Severe hypotension can occur after initial doses of any ACE inhibitor in patients who are hypovolemic due to diuretics, salt restriction, or gastrointestinal fluid loss. Other adverse effects common to all ACE inhibitors include acute renal failure (particularly in patients with bilateral renal artery stenosis or stenosis of the renal artery of a solitary kidney), hyperkalemia, dry cough sometimes accompanied by wheezing, and angioedema. Hyperkalemia is more likely to occur in patients with renal insufficiency or diabetes. Bradykinin seems to be responsible for the cough and angioedema seen with ACE inhibition.

The use of ACE inhibitors is contraindicated during the second and third trimesters of pregnancy because of the risk of fetal hypotension, anuria, and renal failure, sometimes associated with fetal malformations or death. Captopril, particularly when given in high doses to patients with renal insufficiency, may cause neutropenia or proteinuria. Minor toxic effects seen more typically include altered sense of taste, allergic

skin rashes, and drug fever, which may occur in as many as 10% of patients. The incidence of these adverse effects may be lower with the long-acting ACE inhibitors.

Important drug interactions include those with potassium supplements or potassium-sparing diuretics, which can result in hyperkalemia. Nonsteroidal anti-inflammatory drugs may impair the hypotensive effects of ACE inhibitors by blocking bradykinin-mediated vasodilation, which is at least in part, prostaglandin mediated.

ANGIOTENSIN RECEPTOR-BLOCKING AGENTS

Losartan and **valsartan** are recently released blockers of the angiotensin type 1 (AT_1) receptor. They have no effect on bradykinin metabolism and are therefore more selective blockers of angiotensin effects than ACE inhibitors. They also have the potential for more complete inhibition of angiotensin action compared with ACE inhibitors because there are enzymes other than ACE that are capable of generating angiotensin II. Losartan is orally active and extensively metabolized; its principal 5-carboxylic acid metabolite is active. The half-life of losartan is about 2 hours; the half-life of the metabolite is 6–9 hours. The typical starting dosage is 50 mg/d, with a usual dose range of 25–100 mg/d. The side effects are similar to those described for ACE inhibitors, including the hazard of use during pregnancy, with the exception of cough and angioedema, which are thought to be mediated by bradykinin.

Saralasin (1-sar-8-ala-angiotensin II) is an analog and competitive inhibitor of angiotensin II at its receptors (Figure 11–6). Saralasin blocks the pressor and aldosterone-releasing effects of infused angiotensin II and lowers blood pressure in high-renin states such as renal artery stenosis. Saralasin also has weak agonist activity, however, so that rapid injection or administration to persons without high circulating angiotensin II may increase rather than decrease blood pressure. Because it had to be administered by continuous intravenous infusion and because its vascular effects were unpredictable, saralasin was withdrawn from the market. However, this partial agonist drug has proved to be a valuable research tool in determining the role of angiotensin II in hypertension.

II. CLINICAL PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

Hypertension presents a unique problem in therapeutics. It is usually a lifelong disease that causes few symptoms until the advanced stage. For effective treatment, medicines that are expensive and often produce adverse effects must be consumed daily. Thus, the physician must establish with certainty that hypertension is persistent and requires treatment and must exclude secondary causes of hypertension that might be treated by definitive surgical procedures. Persistence of hypertension, particularly in persons with mild elevation of blood pressure, should be established by finding an elevated blood pressure on at least three different office visits. Ambulatory blood pressure monitoring may be the best predictor of risk and therefore of need for therapy in mild hypertension. Recent evidence indicates that isolated systolic hypertension and hypertension in the elderly also benefit from therapy.

Once the presence of hypertension is established, the question of whether or not to treat and which drugs to use must be considered. The level of blood pressure, the age and sex of the patient, the severity of organ damage (if any) due to high blood pressure, and the presence of cardiovascular risk factors must all be considered.

Once the decision is made to treat, a therapeutic regimen must be developed and the patient must be educated about the nature of hypertension and the importance of treatment. Selection of drugs is dictated by the level of blood pressure, the presence and severity of end-organ damage, and the presence of other diseases. Severe high blood pressure with life-threatening complications requires more rapid treatment with more potent drugs. Most patients with essential hypertension, however, have had elevated blood pressure for months or years, and therapy is best initiated in a gradual fashion.

Successful treatment of hypertension requires that dietary instructions be followed and medications be taken as directed. Education about the natural history of hypertension and the importance of treatment as well as potential side effects of drugs is essential. Follow-up visits should be frequent enough to convince the patient that the physician thinks the illness is serious. With each follow-up visit, the importance of treatment should be reinforced and questions particularly concerning dosing or side effects of medication encouraged. Other factors that may improve compliance are simplifying dosing regimens and having the patient monitor blood pressure at home.

OUTPATIENT THERAPY OF HYPERTENSION

The initial step in treating hypertension may be nonpharmacologic. As discussed previously, sodium restriction may be effective treatment for as many as half of patients with mild hypertension. The average American diet contains about 200 meq of sodium per day. A reasonable dietary goal in treating hypertension is 70–100 meq of sodium per day, which can be

achieved by not salting food during or after cooking and by avoiding processed foods that contain large amounts of sodium. Compliance with sodium restriction can be assessed by measuring 24-hour urinary excretion of sodium, which approximates sodium intake, before and after dietary instruction.

Weight reduction even without sodium restriction has been shown to normalize blood pressure in up to 75% of overweight patients with mild to moderate hypertension. Regular exercise has been shown in some but not all studies to lower blood pressure in hypertensive patients.

For pharmacologic management of mild hypertension, blood pressure can be normalized in most patients with a single drug. Such "monotherapy" is also sufficient for some patients with moderate hypertension. Thiazide diuretics and beta-blockers are the only drugs that have been shown to reduce morbidity and mortality and are recommended for initial drug therapy in such patients. There has been concern that diuretics and beta-blockers, by adversely affecting the serum lipid profile or impairing glucose tolerance, may add to the risk of coronary disease, thereby offsetting the benefit of blood pressure reduction. Alternative choices for initial monotherapy include ACE inhibitors, calcium channel blockers, selective α_1 blockers (eg, prazosin), $\alpha + \beta$ blockers (labetalol or carvedilol), and central sympathoplegic agents (eg, clonidine), though none of these have yet been shown to affect long-term outcome. The presence of concomitant disease should influence selection of antihypertensive drugs because two diseases may benefit from a single drug. For example, beta-blockers or calcium channel blockers are particularly useful in patients who also have angina, diuretics or ACE inhibitors in patients who also have congestive heart failure. Race also affects drug selection: blacks respond well to diuretics and calcium channel blockers and less well to beta-blockers and ACE inhibitors.

If a single drug does not adequately control blood pressure, drugs with different sites of action can be combined to effectively lower blood pressure while minimizing toxicity ("stepped care"). If a diuretic is not used initially, it is often selected as the second drug. If three drugs are required, combining a diuretic, a sympathoplegic agent or an ACE inhibitor, and a direct vasodilator (eg, hydralazine or a calcium channel blocker) is often effective.

Assessment of blood pressure during office visits should include measurement of recumbent, sitting, and standing pressures. An attempt should be made to normalize blood pressure (mean blood pressure ≤ 100 mm Hg) in the posture or activity level that is customary for the patient. The extent of orthostatic hy-

MONOTHERAPY VERSUS POLYPHARMACY IN HYPERTENSION

Monotherapy of hypertension (treatment with a single drug) has become more popular since the introduction of ACE inhibitors and α_1-selective alpha-blockers because compliance is likely to be better and because in some cases adverse effects are fewer. However, moderate to severe hypertension is still commonly treated by a combination of two or more drugs, each acting by a different mechanism (polypharmacy). The rationale for polypharmacy is that each of the drugs acts on one of a set of interacting, mutually compensatory regulatory mechanisms for maintaining blood pressure (Figures 6–7 and 11–1).

For example, because an adequate dose of hydralazine causes a significant decrease in peripheral vascular resistance, there will initially be a drop in mean arterial blood pressure, evoking a strong response in the form of compensatory tachycardia and salt and water retention (Figure 11–5). The result is an increase in cardiac output that is capable of almost completely reversing the effect of hydralazine. The addition of a sympathoplegic drug (eg, propranolol) prevents the tachycardia; addition of a diuretic (eg, hydrochlorothiazide) prevents the salt and water retention. In effect, all three drugs increase the sensitivity of the cardiovascular system to each other's actions. Thus, partial impairment of one regulatory mechanism (sympathetic discharge to the heart) increases the antihypertensive effect of impairing regulation by another mechanism (peripheral vascular resistance). Finally, in some circumstances, a normal compensatory response accounts for the toxicity of an antihypertensive agent, and the toxic effect can be prevented by administering a second type of drug. In the case of hydralazine, compensatory tachycardia and increased cardiac output may precipitate angina in patients with coronary atherosclerosis. Addition of the beta-blocker and diuretic can prevent this toxicity in many patients.

In practice, when hypertension does not respond adequately to a regimen of one drug, a second drug from a different class with a different mechanism of action and different pattern of toxicity is added. If the response is still inadequate and compliance is known to be good, a third drug may be added. The drugs least likely to be successful as monotherapy are hydralazine and minoxidil. It is not completely clear why other drugs such as α_1-blockers and calcium channel blockers cause less marked compensatory responses for the same amount of blood pressure lowering.

potension and inhibition of reflex or exercise tachycardia are useful indicators of the effectiveness of or compliance with sympathoplegic therapy. In addition to noncompliance with medication, causes of failure to respond to drug therapy include excessive sodium intake and inadequate diuretic therapy with excessive blood volume (this can be measured directly), and drugs such as antidepressants, nonsteroidal anti-inflammatory drugs, over-the-counter sympathomimetics, and oral contraceptives that can interfere with actions of some antihypertensive drugs or directly raise blood pressure.

MANAGEMENT OF HYPERTENSIVE EMERGENCIES

Despite the large number of patients with chronic hypertension, hypertensive emergencies are relatively rare. Marked or sudden elevation of blood pressure may be a serious threat to life, however, and prompt reduction of blood pressure is indicated. Most commonly, hypertensive emergencies occur in patients whose hypertension is severe and poorly controlled and in those who suddenly discontinue antihypertensive medications.

Clinical Presentation & Pathophysiology

Hypertensive emergencies include hypertension associated with vascular damage (termed malignant hypertension) and hypertension associated with hemodynamic complications such as cardiac failure, stroke, or dissecting aneurysm. The underlying pathologic process in malignant hypertension is a progressive arteriopathy with inflammation and necrosis of arterioles. Vascular lesions occur in the kidney, which releases renin, which in turn stimulates production of angiotensin and aldosterone, which further increase blood pressure.

Hypertensive encephalopathy is a classic feature of malignant hypertension. Its clinical presentation consists of severe headache, mental confusion, and apprehension. Blurred vision, nausea and vomiting, and focal neurologic deficits are common. If untreated, the syndrome may progress over a period of 12–48 hours to convulsions, stupor, coma, and even death.

Treatment of Hypertensive Emergencies

The general management of hypertensive emergencies requires monitoring the patient in an intensive care unit with continuous recording of arterial blood pressure. Fluid intake and output must be monitored carefully and body weight measured daily as an indicator of total body fluid volume during the course of therapy.

Parenteral antihypertensive medications are used to lower blood pressure rapidly (within a few hours); as soon as reasonable blood pressure control is achieved, oral antihypertensive therapy should be substituted, because this allows smoother long-term management of hypertension. The goal of treatment in the first few hours or days is not normalization of blood pressure because chronic hypertension is associated with autoregulatory changes in cerebral blood flow. Thus, rapid normalization of blood pressure may lead to cerebral hypoperfusion and brain injury. Rather, blood pressure should be lowered by about 25%, maintaining diastolic blood pressure at no less than 100–110 mm Hg. Subsequently, blood pressure can be reduced to normal levels using oral medications over several weeks. The drugs most commonly used to treat hypertensive emergencies are the vasodilators sodium nitroprusside and diazoxide. Other parenteral drugs that may be effective include nitroglycerin, labetalol, calcium channel blockers, hydralazine, reserpine, and methyldopa. Nonparenteral therapy with oral nifedipine, captopril, prazosin, or clonidine has also been shown to be useful in the therapy of severe hypertension.

Most patients with severe hypertension have a normal or contracted blood volume, although some, eg, those with renal failure, may be hypervolemic. Diuretics are administered to prevent the volume expansion that typically occurs during administration of powerful vasodilators. Because it is likely that the patient will have compromised renal function, a drug that works in the presence of renal insufficiency, such as furosemide, should be selected.

Dialysis may be a necessary alternative to the loop diuretics, particularly in patients with oliguric renal failure. Dialysis can remove excess fluid, correct electrolyte disturbances, and control symptoms of uremia. Uremic symptoms may be confusing in evaluating patients with hypertensive encephalopathy.

PREPARATIONS AVAILABLE

Beta-Adrenoceptor Blockers

Acebutolol (Sectral)
Oral: 200, 400 mg capsules

Atenolol (generic, Tenormin)
Oral: 25, 50, 100 mg tablets
Parenteral: 0.5 mg/mL for injection

Betaxolol (Kerlone)
Oral: 10, 20 mg tablets

Bisoprolol (Zelate)
Oral: 5, 10 mg tablets

Carteolol (Cartrol)
Oral: 2.5, 5 mg tablets

Carvedilol (Coreg)
Oral: 6.25, 12.5, 25 mg tablets
Labetalol (Normodyne, Trandate)
Oral: 100, 200, 300 mg tablets
Parenteral: 5 mg/mL for injection
Metoprolol (Lopressor)
Oral: 50, 100 mg tablets
Oral extended release (Toprol-XL): 50, 100, 200 mg tablets
Parenteral: 1 mg/mL for injection
Nadolol (Corgard)
Oral: 20, 40, 80, 120, 160 mg tablets
Penbutolol (Levatol)
Oral: 20 mg tablets
Pindolol (generic, Visken)
Oral: 5, 10 mg tablets
Propranolol (generic, Inderal)
Oral: 10, 20, 40, 60, 80, 90 mg tablets; Intensol, 80 mg/mL solution
Oral sustained-release (generic, Inderal LA): 60, 80, 120, 160 mg capsules
Parenteral: 1 mg/mL for injection
Timolol (generic, Blocadren)
Oral: 5, 10, 20 mg tablets

Centrally Acting Sympathoplegic Drugs

Clonidine (generic, Catapres)
Oral: 0.1, 0.2, 0.3 mg tablets
Transdermal (Catapres-TTS): patches that release 0.1, 0.2, 0.3 mg/24 hr
Guanabenz (Wytensin)
Oral: 4, 8 mg tablets
Guanfacine (Tenex)
Oral: 1, 2 mg tablets
Methyldopa (generic, Aldomet)
Oral: 125, 250, 500 mg tablets; 250 mg/5 mL suspension
Parenteral: 250 mg/5 mL for injection

Postganglionic Sympathetic Nerve Terminal Blockers

Guanadrel (Hylorel)
Oral: 10, 25 mg tablets
Guanethidine (generic, Ismelin Sulfate)
Oral: 10, 25 mg tablets
Reserpine (generic, Serpasil)
Oral: 0.1, 0.25 mg tablets

Alpha$_1$-Selective Adrenoceptor Blockers

Doxazosin (Cardura)
Oral 1, 2, 4, 8 mg tablets
Prazosin (Minipress)
Oral: 1, 2, 5 mg capsules
Terazosin (Hytrin)
Oral: 1, 2, 5, 10 mg tablets; 1, 2, 5, 10 mg capsules

Ganglion Blocking Agents

Mecamylamine (Inversine)
Oral: 2.5 mg tablets

Vasodilators Used in Hypertension

Diazoxide (generic, Hyperstat IV)
Oral (Proglycem): 50 mg capsule; 50 mg/mL oral suspension
Parenteral: 15 mg/mL, 300 mg/20 mL amp
Hydralazine (generic, Apresoline)
Oral: 10, 25, 50, 100 mg tablets
Parenteral: 20 mg/mL for injection
Minoxidil (generic, Loniten)
Oral: 2.5, 10 mg tablets
Topical (Rogaine, etc): 1.8 g/60 mL lotion
Nitroprusside (generic, Nipride)
Parenteral: 50 mg/vial

Calcium Channel Blockers

Amlodipine (Norvasc)
Oral 2.5, 5, 10 mg tablets
Diltiazem (generic, Cardizem)
Oral: 30, 60, 90, 120 mg tablets (unlabeled in hypertension)
Oral sustained-release (Cardizem CD, Cardizem SR, Dilacor XL): 60, 90, 120, 180, 240, 300 mg capsules
Parenteral: 5 mg/mL for injection
Felodipine (Plendil)
Oral extended release: 2.5, 5, 10 mg tablets
Isradipine (DynaCirc)
Oral: 2.5, 5 mg capsules
Nicardipine (Cardene)
Oral: 20, 30 mg capsules
Oral sustained release (Cardene SR): 30, 45, 60 mg capsules
Parenteral (Cardene IV): 25 mg/mL for injection
Nisoldipine (Sular)
Oral: 10, 20, 30, 40 mg tablets
Nifedipine (generic, Adalat, Procardia)
Oral: 10, 20 mg capsules (unlabeled in hypertension)
Oral extended-release (Adalat CC, Procardia-XL): 30, 60, 90 mg tablets
Verapamil (generic, Calan, Isoptin)
Oral: 40, 80, 120 mg tablets
Oral sustained-release (generic, Calan SR, Verelan): 120, 180, 240 mg tablets; 120, 180, 240 mg capsules
Parenteral: 5 mg/2 mL for injection

Angiotensin-Converting Enzyme Inhibitors

Benazepril (Lotensin)
Oral: 5, 10, 20, 40, mg tablets
Captopril (Capoten)
Oral: 12.5, 25, 50, 100 mg tablets

Enalapril (Vasotec)
Oral: 2.5, 5, 10, 20 mg tablets
Parenteral (Enalaprilat): 1.25 mg/mL for injection
Fosinopril (Monopril)
Oral: 10, 20 mg tablets
Lisinopril (Prinivil, Zestril)
Oral: 2.5, 5, 10, 20, 40 mg tablets
Moexipril (Univase)
Oral: 7.5, 15 mg tablets
Quinapril (Accupril)
Oral: 5, 10, 20, 40 mg tablets
Perindopril (Aceon)
Oral: 2, 4, 8 mg tablets
Ramipril (Altace)
Oral: 1.25, 2.5, 5, 10 mg capsules

Angiotensin Receptor Blockers
Losartan (Cozaar)
Oral: 25, 50 mg tablets
Valsartan (Diovan)
Oral: 80, 160 mg tablets

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